REMARKS/ARGUMENTS

I. Status of the Claims

Claims 1 and 60-77 are currently pending in this application. Upon entry of this amendment, claims 1, 66 and 69-73 are withdrawn, claims 60-62 and 75 are amended, and new claims 78 and 79 are added. Claims 60-65, 67-68 and 74-79, and withdrawn claims 1, 66 and 69-73, are thus pending following entry of this amendment.

The claims have been amended to be directed to a method of diagnosing a hyper-proliferative disorder. Support for the present claims is provided in original claims 34 and 35, in the specification at, e.g., page 4, lines 1-4, page 31, lines 16 to page 33, line 23, and page 39, line 34 to page 41, line 2. Examples of such hyper-proliferative disorders include cancers, precancers (e.g., cervical dysplasia), and abnormal cells that are not yet cancerous (e.g., psoriasis), and a wide variety of disease states associated with abnormal cellular proliferation (see list on page 38, line 16 to page 39, line 33).

Claim 60 has been amended. Support is provided in original claim 34 and in the specification at, e.g., page 4, lines 1-4.

Claim 60 has been amended to replace "KSP" with "kindle-like spindle protein (KSP)." Support is provided in the specification at, e.g., page 7, line 50 in GenBank Accession No. U37426, which is incorporated by reference at page 50, lines 28-30.

Claim 61 has been amended for clarity.

Claim 62 has been amended to correct an inadvertent omission.

Claim 75 has been amended to replace "is at risk for the hyper-proliferative disorder" with "has a hyper-proliferative disorder." Support is provided in the specification at, e.g., page 39, line 34 to page 41, line 2.

New claim 78 is added. Support is provided in the specification at, e.g., page 31, line 16 to page 33, line 23.

New claim 79 is added. Support is provided in original claim 35 and in the specification at, e.g., page 31, lines 16 to page 33, line 23.

No new matter is added by these amendments and new claims. No amendment should be construed as acquiescence in the rejection.

II. Formalities

The Examiner alleges the priority date of the instant application is June 19, 2003, the filing date, because the parent application allegedly does not reveal support for the claimed invention. Applicants have amended the claims to be directed to a method of diagnosing a hyper-proliferative disorder as disclosed and claimed in the parent application. Particularly as amended, it is respectfully submitted that the priority date of the instant application is October 27, 1999, the filing date of the parent application.

III. Specification

As requested by the Examiner, Applicants have amended page 1 of the specification to reflect the status of the parent application.

The Examiner objected to the specification as allegedly failing to provide proper antecedent basis for the claimed subject matter. Applicants have amended the claims to be directed to a method of diagnosing a hyper-proliferative disorder thereby obviating this ground of objection to the specification.

III. Claim Rejections Under 35 U.S.C. § 112

1. Indefiniteness

Claims 60-65, 67-68 and 74-77 are rejected as allegedly being indefinite. In particular, the Examiner alleges that the use of the KSP designation as the sole means to identify the claimed gene renders claims 60-65, 67-68 and 74-77 indefinite. The Examiner also alleges that claims 60, 62-65, 67-68 and 74-77 are incomplete for omitting the essential step of determining which comparison result in step (b) results in the assessment of risk of a hyper-proliferative disorder in step (c).

Regarding the use of the KSP designation, Applicants have amended claims 60 and 62 unambiguously to define KSP as kindle-like spindle protein, thereby obviating this ground of rejection of these claims.

Regarding the allegedly omitted essential step, Applicants have amended claims 60 and 62 to recite that an increase in the expression of KSP, or at least one of the plurality of target molecules including KSP, in the sample as compared to the control indicates that the individual has a hyper-proliferative disorder. Accordingly, particularly as amended, the present claims do not omit an essential step.

2. Enablement

Claims 60-65, 67-68 and 74-77 are rejected as allegedly lacking enablement. The Examiner alleges that the specification does not enable one of skill in the art to make and use the invention because the specification does not: (1) provide any guidance on differential expression of KSP in individuals at risk for a hyper-proliferative disorder; (2) provide any guidance on which hyper-proliferative disorders can be predictably assessed for risk; (3) establish a correlation between the expression level of KSP and the assessment of an individual's risk for a hyper-proliferative disease; and (4) provide any evidence that differential expression of KSP is associated with a hyper-proliferative disorder or an individual's risk for a hyper-proliferative disorder. The Examiner alleges that, given the necessity to validate disease markers and the lack of concrete examples in the specification, the skilled artisan would not believe it is more likely than not that the invention will function as claimed with a reasonable expectation of success, and

that undue experimentation would be required to practice the claimed invention. Applicants respectfully traverse this rejection as it may be applied to the claims as amended.

The presently claimed invention is directed to a method of diagnosing a hyper-proliferative disorder by determining the expression level of KSP, or the expression levels of a plurality of target molecules including KSP, in a sample from an individual, and comparing the expression level of KSP with a control of known proliferation state (e.g., normal cells not in a hyper-proliferative state), wherein an increase of expression level of KSP in the sample as compared to the control indicates that the individual has a hyper-proliferative disorder. The presently claimed invention is based, in part, on Applicants' discovery that KSP is up-regulated at the mRNA level in tumor tissue from breast, lung and colon as compared to matched normal tissue (see Figure 1).

The Examiner acknowledges that the specification teaches that expression levels of KSP can be assessed at the gene or polypeptide level. The specification also teaches that KSP mRNA levels are elevated in human cancer tissue from breast, lung and colon as compared to matched normal (i.e., non-cancer) tissue. In particular, KSP expression was shown to be 6- to 44-fold higher in cancer as compared to non-cancer tissues. Because it is well-known that cancer cells over-proliferate as compared to non-cancer cells, the elevated expression of KSP in a sample provides an indication of the presence of a hyper-proliferative disorder.

The Examiner alleges that the specification lacks guidance and evidence with respect to assessing an individual's risk for a hyper-proliferative disorder based on the expression level of KSP. Without agreeing with the Examiner's allegation, Applicants have amended the claims to be directed to a method of diagnosing a hyper-proliferative disorder. As discussed above, the specification provides (1) guidance on how to determine the expression level of KSP or a plurality of target molecules in a sample obtained from an individual and (2) evidence on the differential expression of KSP in individuals that have a hyper-proliferative disorder, e.g., cancer. The example in the specification establishes the correlation between the relative expression level of KSP and presence of a hyper-proliferative disorder, e.g., cancer. The

specification at page 38, line 16 to page 39, line 33 provides a list of diseases, disorders and conditions that are associated with a hyper-proliferative state. The skilled artisan would recognize that Applicants' finding of increased expression of KSP mRNA in three cancer tissues can be translated to other cancers and hyper-proliferative disorders associated with abnormal cellular proliferation because of the known critical role of KSP in this process. As described in the specification at page 7, lines 3-10, the microinjection of an antibody to KSP into proliferating cells causes mitotic arrest. Thus, based on the teachings of the specification and the knowledge in the art, the skilled artisan would believe that increased KSP expression is associated with cellular proliferation and, hence, hyper-proliferative disorders. Accordingly, the skilled artisan would believe that it is more likely than not that the diagnostic methods of the presently claimed invention can be practiced as claimed without undue experimentation.

The Examiner cites Tockman et al. (Cancer Res. 52:2711s-2718s, 1992) as discussing considerations that are necessary to bring (hyper-proliferation disorder) biomarkers to clinical application. Based on Tockman's teaching, the Examiner alleges that such biomarkers must be validated by providing or establishing a correlation with the disease or risk of disease. It is respectfully submitted that the experimental data provided in the specification provides the requisite correlation between the expression level of KSP and presence of a hyper-proliferative disorder. Other cellular proliferation sequences that are up-regulated during cellular proliferation and associated with hyper-proliferative disorders, suitable for use in the claimed methods, are already known in the art.

Based on the foregoing, Applicants respectfully request that the rejection of claims 60-65, 67-68 and 74-77 as lacking enablement be withdrawn.

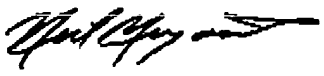
3. Improper dependent form

Claims 62 and 63 are rejected as allegedly being of improper dependent form by failing to further limit the subject matter of claim 60. Applicants disagree. Independent claim 60 is drawn to a method of diagnosing a hyper-proliferative disorder comprising determining the

expression level of KSP in a sample from an individual and comparing the expression level of KSP in the sample with the expression level of KSP in a control. Determination of additional target molecules is neither required nor excluded by such methods. Dependent claim 62 further limits the subject matter of claim 60 by requiring that the determining and comparing steps include determining and comparing the expression level of a plurality of target molecules in addition to KSP. Thus, claim 62 limits rather than broadens claim 60. Accordingly, no amendment of claims 62 and 63 is required.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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